

Graylands Hospital Drug Bulletin

Desvenlafaxine and Duloxetine - new antidepressants

North Metropolitan Area Health Service-Mental Health March 2009 Vol 16 No.1 ISSN 1323-1251

Desvenlafaxine and Duloxetine

Desvenlafaxine (Pristiq®) and duloxetine (Cymbalta®) have recently been approved for the treatment of major depressive disorder (MDD). They belong to the same class of antidepressant as venlafaxine, as they are both serotonin and noradrenaline reuptake inhibitors (SNRIs). Serotonin and noradrenaline both contribute to the pathology and treatment of depression.^{1, 2} Serotonin affects areas of the brain that control mood, impulsivity, aggression, appetite and sexual function, and noradrenaline affects areas of the brain controlling mood, concentration and motivation.² By increasing the levels of both neurotransmitters, different target symptoms may be treated, thereby having a theoretical synergistic effect. A description of the therapeutic profile of duloxetine and desvenlafaxine is included overleaf. Table 1 compares the pharmacological profile of desvenlafaxine and duloxetine with other antidepressants.

Place in therapy

Non-pharmacological therapies are recommended as first-line treatment strategies for mild depression.³ Antidepressants are equally effective as psychological therapies for moderate depression.^{3,9} The antidepressants that are recommended as first-line treatment options for the treatment of MDD are the Selective Serotonin Reuptake Inhibitors (SSRIs), SNRIs, mirtazapine, moclobemide and reboxetine, and as such, duloxetine and desvenlafaxine are new first-line treatment options for MDD.^{3, 6}

It is not known if these new antidepressants have any advantages over existing therapies in clinical practice. It is not currently possible to predict which patients will respond to which antidepressant. Therefore, choice of antidepressant for an individual patient will depend on its adverse effect profile, potential for drug interactions and safety.^{3, 7}

General Precautions

Duloxetine and desvenlafaxine have general precautions that are common to many antidepressants and are discussed below. Precautions that are specific to each agent are discussed under the relevant drug heading.

Clinical worsening and suicide risk

As with other antidepressants, patients prescribed duloxetine and desvenlafaxine should be monitored for clinical worsening and suicidality, particularly on initiation or with dose changes.^{1, 10} Caution is also required in patients with a history of bipolar disorder, as activation of mania may occur during therapy.¹

Children and adolescents

Some antidepressants have been linked to an increased risk of suicidal thinking and behaviour in children and adolescents with MDD. Clinical trials for duloxetine and desvenlafaxine have not been conducted in children or adolescents and they are not approved for use in this population and should be avoided.¹

Concomitant illness

As duloxetine and desvenlafaxine have not been systematically studied in a range of physical illnesses, caution is required especially in patients with seizure disorders, recent myocardial infarction or unstable heart disease.¹ Caution is required in patients with acute narrow angle glaucoma, as both agents have been reported to cause mydriasis.¹

Drug interactions

Duloxetine and desvenlafaxine are contraindicated in patients taking monoamine oxidase inhibitors (MAOIs).¹ Patients taking MAOIs must have a washout period of at least 14 days before commencing either antidepressant. Patients switching to a MAOI must have a washout period of at least 5 days for duloxetine, and at least 7 days for desvenlafaxine.¹

Both antidepressants should be used with caution with other serotonergic agents such as antidepressants, stimulants, 5HT1 agonists and some opioids, as the risk of developing serotonin syndrome may be increased.¹

	Desvenlafaxine	Duloxetine
Clinical efficacy	<p>The efficacy of desvenlafaxine in MDD has been established in four, 8-week, randomised, double-blind, placebo-controlled, fixed-dose trials.¹¹⁻¹⁵ The dose used in the trials ranged between 50-400mg daily. In all of these studies, patients receiving desvenlafaxine demonstrated greater improvement in the HAMD-17 total score than did patients receiving placebo. Patients receiving desvenlafaxine also demonstrated greater overall improvement as measured by the Clinical Global Impressions Scale-Improvement (CGI-I) compared with patients receiving placebo in 3 out of 4 studies. There was no additional benefit in using doses greater than 50mg, and adverse effects and drug discontinuances were reported more frequently at higher dosages of the desvenlafaxine.</p> <p>Desvenlafaxine has not been directly compared to currently available antidepressants in terms of efficacy. However, the Pharmaceutical Benefits Advisory Committee (PBAC) has indirectly compared desvenlafaxine with venlafaxine and has recommended listing on the Pharmaceutical Benefits Scheme (PBS) on a cost-minimisation basis.¹⁶ According to the PBAC analysis, desvenlafaxine 50mg is equi-effective to venlafaxine 75mg. It is not known if desvenlafaxine offers any clinical advantages over existing therapies.</p>	<p>Efficacy of duloxetine for depression has been established in controlled studies of 8-9 weeks' duration in adults in outpatient settings.⁴⁻⁹ Patients receiving duloxetine (40-120 mg daily) had greater improvements in the 17-item Hamilton depression rating scale (HAMD-17) total score than did patients receiving placebo.⁴⁻⁹ Duloxetine has been compared to venlafaxine and escitalopram in clinical trials. The results of three studies comparing duloxetine 60-120mg daily with escitalopram 10-20mg daily have been inconsistent; duloxetine showed non-inferiority in one short-term study and inferiority to escitalopram in another.^{10, 17} In a third long-term study, there was no difference between the duloxetine and escitalopram groups.¹⁸ The pooled results of two venlafaxine and duloxetine trials showed that duloxetine 60 mg daily had similar efficacy to venlafaxine 150 mg daily after 6 weeks.¹⁹ Duloxetine has shown efficacy in the treatment of generalised anxiety disorder, neuropathic pain and stress urinary incontinence, although it is not approved for these indications in Australia.²⁰</p>
Pharmacokinetics	<p>Key pharmacokinetic data for desvenlafaxine: Bioavailability= 80%; Volume of distribution= 3.4L/kg; Half-life= 11 hours; Time to maximum concentration= 7.5 hours; Protein binding= 30%. Desvenlafaxine undergoes minimal metabolism via the CYP 450 isoenzymes and 45% of the dose is excreted unchanged in the urine.¹</p>	<p>Key pharmacokinetic data for duloxetine: bioavailability= 50%; Volume of distribution= 1640L; half-life= 12.1 hours; time to maximum concentration= 6 hours; protein binding= >90%. Duloxetine undergoes extensive hepatic metabolism via cytochrome P450 2D6 and 1A2 to form inactive metabolites, which are excreted primarily via urine.¹ Duloxetine itself is a moderately potent inhibitor of CYP 2D6.¹</p>
Dosage and administration	<p>Commencing desvenlafaxine The recommended dose of desvenlafaxine is 50mg daily. Although studies have shown efficacy of desvenlafaxine over placebo in doses of up to 400mg daily, no additional benefit was observed in doses above 50mg daily. The maximum licensed dose of desvenlafaxine is 200mg daily.¹ In patients with severe renal impairment (creatinine clearance <30mL/min), a dose of 50mg every second day is recommended.¹ No dosage adjustment is necessary based solely on age. However, the possibility of reduced renal clearance should be considered when determining the dose of desvenlafaxine. Dose adjustments are not required in patients with hepatic impairment.¹ Desvenlafaxine is formulated in an extended release tablet and should be swallowed whole. Patients should be advised that the inert tablet matrix might be visible in the stools.¹</p> <p>Discontinuing desvenlafaxine As with venlafaxine, discontinuation effects can be problematic for many patients ceasing desvenlafaxine. A gradual reduction in dose with close monitoring is suggested. Although not studied for desvenlafaxine, switching to a long-acting SSRI such as fluoxetine may alleviate antidepressant discontinuation effects for some patients.²²</p>	<p>Commencing duloxetine Duloxetine is formulated in an enteric-coated capsule that must be swallowed whole in order to prevent degradation of duloxetine into inactive compounds, which would result in lack of therapeutic effect and gastric irritation. Duloxetine can be administered without regard to food, however administration with food may reduce nausea. The suggested starting dose for duloxetine is 60mg daily.¹ However, for patients in whom initial tolerability may be a concern, a starting dose of 30mg daily for one week may be warranted.¹ There is no evidence to suggest that patients will benefit from doses greater than 60mg daily.^{1, 23} A dose of 30mg daily is recommended for patients with end stage renal disease (creatinine clearance < 30 mL/minute). Dose reductions are generally not required for elderly patients unless there is renal impairment.</p> <p>Discontinuing duloxetine Discontinuation effects can be troublesome for many patients, particularly if therapy has continued for greater than one month. It is recommended that duloxetine dose be halved for two or more weeks before discontinuation, or alternatively dosed every second day.¹</p>
Drug interactions	<p>As desvenlafaxine is primarily metabolised through conjugation, drugs that affect the CYP 450 isoenzymes are unlikely to have a significant effect on desvenlafaxine levels. Desvenlafaxine is a weak inhibitor of the CYP 2D6 isoenzyme, and hence may increase the levels of drugs metabolised via this pathway.¹</p>	<p>Duloxetine is contraindicated in patients that are taking concomitant medications that are strong inhibitors of CYP450 1A2, as these can increase the plasma levels of duloxetine.¹ As duloxetine moderately inhibits CYP 2D6, some drugs that are predominantly metabolised by this isoenzyme may be affected.</p>
Contraindications/Precautions	<p>There are no contraindications for desvenlafaxine in addition to the concomitant use with MAOI antidepressants as described in the shared precautions/contraindications.¹</p>	<p>In addition to the contraindications in common with desvenlafaxine and other antidepressants, there have been post-marketing reports of hepatic injury (including hepatitis and cholestatic jaundice) with duloxetine. Evidence suggests that patients with pre-existing liver disease who take duloxetine may have an increased risk for further liver damage; as a result, duloxetine is contraindicated in patients with liver disease, and should be avoided in patients with substantial alcohol consumption.¹</p>
Pregnancy and lactation	<p>The safety of desvenlafaxine in pregnancy and lactation has not been established. The ADEC lists desvenlafaxine as category B2 in pregnancy; teratogenic effects are not expected, but foetal harm may occur.¹ As desvenlafaxine is excreted in breast milk, the manufacturers advise that desvenlafaxine should only be used if the benefits outweigh the risks.¹</p>	<p>The safety of duloxetine in pregnancy and lactation has not been established. The ADEC lists duloxetine as category B3 in pregnancy; teratogenic effects are not expected, but foetal harm may occur.¹ In lactating mothers, the estimated infant dose ranges from approximately 0.1 to 0.3% of the maternal dose.¹ Due to the risk of adverse effects in the neonate, the manufacturers advise against the use of duloxetine in lactation.¹</p>
Adverse effects	<p>The adverse effect profile of desvenlafaxine is similar to that of venlafaxine. The most common adverse effects reported in the clinical trials were nausea, insomnia, somnolence and dizziness.¹ Due to its noradrenergic action, desvenlafaxine may increase blood pressure and heart rate during therapy.² Desvenlafaxine may raise cholesterol and triglyceride levels and monitoring is suggested. Other notable adverse effects that may occur include: diarrhoea, anxiety, sexual dysfunction, abnormal bleeding and hyponatraemia.¹</p>	<p>The adverse effects reported for duloxetine in clinical trials were very similar to those of venlafaxine. Nausea, headache, dry mouth, constipation, excessive sweating, and dizziness were the most frequently reported adverse effects.²³ However, there were significantly more reports of nausea, severe nausea and dizziness with duloxetine than with venlafaxine in the first 6-weeks of therapy.²³ Other notable adverse effects that occur with SSRI/SNRI antidepressants that may also occur with duloxetine include: diarrhoea, insomnia, anxiety, sexual dysfunction, abnormal bleeding and hyponatraemia.² Due to duloxetine's noradrenergic action, increased blood pressure and increased heart rate may occur as an adverse effect.²</p>
Prescribing information	<p>Desvenlafaxine (Pristiq®) is available on the PBS for the treatment of MDD. The 50mg and 100mg extended-release tablets are available in packs of 28 with 5 repeats allowable.²⁴</p>	<p>Duloxetine (Cymbalta®) is available on the PBS for treatment of MDD.²⁴ The 60mg enteric-coated capsules are available in packs of 28 with 5 repeats allowable and the 30mg enteric-coated capsules are available in packs of 28 with nil repeats allowed.²⁴</p>

Table 1: Pharmacological profile of first-line antidepressants^{1, 22}

	NE	5-HT	DA	ACh	H ₁	α1	α2	
Citalopram	+	++++	-	+	++	+	+-	Key NE=noradrenaline reuptake inhibition ▪ Antidepressant effect ▪ Adverse effects: tremor, tachycardia, sweating, insomnia, sexual dysfunction 5-HT= serotonin reuptake inhibition ▪ Antidepressant and anti-anxiety effect ▪ Adverse effects: nausea, anxiety, sexual dysfunction DA= dopamine reuptake inhibition ▪ Antidepressant and enhanced/motivation/cognition ▪ Adverse effects: activation, psychosis ACh= acetylcholine blockade Adverse effects: dry mouth, blurred vision, urinary retention, constipation, confusion, tachycardia H ₁ = histamine blockade α ₁ = alpha-1 blockade Adverse effects: postural hypotension, dizziness α ₂ = alpha-2 blockade Adverse effects= sexual dysfunction Affinity for receptors: 1/Ki (M)<0.001=-; 0.001-.01=+; 0.01-.1=++; 0.1-1=+++; 1-10=++++; 10-100=+++++; 100-1000=++++++ Affinity for receptors determines pharmacological profile, but may not correlate with clinical efficacy or frequency/severity of adverse effects.
Desvenlafaxine	++	+++	+-	-	-	-	-	
Duloxetine	+++++	+++++	++	+	+	+	-	
Escitalopram	+	++++	-	+	+	+	+-	
Fluoxetine	++	++++	+	++	+	+	+-	
Fluvoxamine	++	++++	+-	+-	-	+	+	
Mirtazapine	+	+	-	++	+++++	++	+++	
Paroxetine	+++	+++++	+	++	+-	+	+	
Sertraline	++	++++	++	++	+-	++	+	
Venlafaxine	++	++++	+	-	-	-	+-	

Conclusions

Response to antidepressants in MDD is highly variable and generally, only a third of patients achieve remission on any antidepressant. Although duloxetine and desvenlafaxine do not have a novel mechanism of action, they do provide clinicians with more first-line treatment options for patients with MDD. At this stage, it is not known which patients will respond to these new agents, nor is it known if these new agents provide any clinical advantages.

New Formulations

Quetiapine XR

Extended release quetiapine (Seroquel XR®) is a new formulation of quetiapine which is now available on the Pharmaceutical Benefits Scheme (PBS) for schizophrenia.²³ It is available in 50mg, 200mg, 300mg and 400mg strengths. It has been introduced to simplify treatment and improve compliance with once-daily dosing of quetiapine. The dose of quetiapine XR can be rapidly initiated with 300mg on day 1, 600mg on day 2 and 800mg on day 3.^{1, 25}

The pharmacokinetics of Quetiapine XR are comparable to the Immediate Release (IR) formulation. Time to maximum concentration is 6 hours (vs. 1 hour for IR), but at the same daily dose the daily exposure of the drug is the same as quetiapine IR dosed twice daily. The elimination half-life of quetiapine XR is 7 hours, similar to that of IR.²⁵ It is recommended that quetiapine XR be given without food.¹

Early studies suggest that quetiapine XR is generally well tolerated and has a similar side-effect profile to quetiapine IR. No unexpected adverse effects have been reported with quetiapine XR.²⁵

Clozapine Suspension

A clozapine (Clopine®) 50mg/mL suspension has recently been added to the PBS Section 100.²³ The suspension requires shaking for 90 seconds at least 24 hours prior to the first dose being issued. Prior to each dose, the bottle must be shaken for a further 10 seconds to ensure even distribution of active ingredient. Clopine® suspension can be used for 90 days after opening. It should be given undiluted, but can be mixed with water should the need arise.²⁶

This bulletin was written by Karolinka Golebiewski and Katie Walker and reviewed by Graylands Pharmacy Department and Dr Rajan Iyyalol

References available on request

Comments are welcome at the email address: DrugInformation.Graylands@health.wa.gov.au